UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,325	07/12/2004	Andreas Finke	RDID01062CUS	8527

23690 7590 04/11/2006

Roche Diagnostics Corporation, Inc.
9115 Hague Road
PO Box 50457
Indianapolis, IN 46250-0457

EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,325	FINKE ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/21/06 has been entered. Claim 1 has been amended. Claims 1-3 and 5 are currently pending.

Rejections Withdrawn

1. The objections to the drawings are withdrawn in light of the replacement drawings submitted 2/21/06.

2. The rejection of claim 1 under 35 USC 112, 2nd paragraph set forth in the previous Office action is withdrawn in light of Applicant's amendments. However, the amended claim presents new grounds of rejection under this statute as set forth below.

Claim Objections

3. Claim 1 is objected to because of the following informalities:

The claim recites "adjusting the pH...**to 10.5 to 12.5**". The language is grammatically awkward. It is suggested that the claim recite "adjusting the pH...**to between 10.5 and 12.5**".

It is suggested that at the first reference to "microparticles" in the body of the claim (part (a)) that the adjective "polystyrene" be included in order to maintain consistency with the preamble of the claim, which recites a method for producing protein-coated **polystyrene** microparticles.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant's amendment, filed 2/21/06 asserts that no new matter has been added and indicates that support for the amendments to claim 1 may be found in the specification in Examples 1 and 2 at paragraphs 45-46.

Claim 1 as originally filed recited combining a suspension of uncoated microparticles with a protein, where the suspension comprised a buffer having a pH of 10 to 12.5. The specification discloses that the coating reaction is preferably carried out at a pH between 10 and 12.5 at [0015].

The claims now recite the step of adjusting the pH of the combination (of microparticles and protein) to between pH 10.5 to 12.5.

First, with regard to the pH range claimed, the specification discloses a general teaching that the coating reaction is carried out at pH **10-12.5** [0015]. The specification also discloses the range of pH **10.5-12.5** at [0030]. However, when this particular pH range of 10.5-12.5 is mentioned, it is in the context of coating intervals of 4-7 days:

It is particularly preferable to carry out the coating for 4 - 7 days. When using these relatively long time intervals, pH ranges of 10.5 to 12.5 and in particular of 11.0 to 12.0 are particularly preferred.

Claim 1 now recites a pH range of 10.5-12.5 and incubating "for a period of time", but makes no mention of a time interval of 4-7 days. This represents new matter because the claim is now drawn to a broad genus of methods carried out at pH 10.5-12.5, which could be carried out for any "period of time", which is broader in scope than the disclosure, which teaches only pH 10.5-12.5 in the context of a 4-7 day coating. In other words, Applicant's incorporation of the pH limitation of 10.5-12.5 without the accompanying limitation of 4-7 days disclosed in the specification has effectively created a new subgenus (pH 10.5-12.5) that is not supported by either the generic teaching (pH 10-12.5) or by the specific teaching (pH 10.5-12.5 with 4-7 day coating). Disclosure of a genus and species of subgenus within that genus is not sufficient description of subgenus to satisfy description requirement of 35 U.S.C. 112, unless there are specific facts which lead to determination that subgenus is implicitly described. Ex parte Westphal, 26 USPQ2d (BPAI 1993). In re Smith 173 USPQ 679 (CCPA 1972).

Second, with regard to the step of adjusting the pH of the combination from 10.5 to 12.5, Applicant indicated that the specification provides support for this limitation at Examples 1-2. In Example 1, [0045], the specification discloses that following combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin, the pH was then adjusted to the desired value between pH 10.0 and pH 12.5 with NaOH. Similarly, at [0046], the specification discloses that following the combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin, the pH was then adjusted to the desired value between pH 10.0 and pH 12.5 with NaOH. Thus, the specification discloses the step of adjusting the pH only in the context of

adjusting the pH of a combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin to between pH 10.0 and pH 12.5. Note that in the specific examples in which the pH is adjusted, it is adjusted to between 10 and 12.5 and not to between 10.5 and 12.5 as now recited in claim 1.

The incorporation of the step of adjusting the pH into claim 1 has effectively created a new subgenus (adjusting the pH of the combination of microparticles with a protein, and adjusting the pH by any means) that is not supported by the specific teaching of particular types of microparticles, a particular protein, and a particular pH range (adjusting the pH of the combination of DYNAL M-270 or M-280 magnetic beads with polymerized streptavidin to between pH 10.0 and pH 12.5 with NaOH). There is also no support in the specification for the step of adjusting the pH to between **10.5** and 12.5 since the specification only discloses adjusting the pH to between 10 and 12.5.

Claim 2 as originally filed recited that the protein is in a polymerized form. The amendment filed 10/6/05 amended the claim to recite that the protein has been polymerized by chemical treatment. Applicant indicated that support may be found for this limitation in the specification at [0027] (see Applicant's response of 10/6/05 at p. 6). Upon reconsideration by the Examiner, this limitation is deemed to represent new matter. The specification at [0027] states that:

Polymerization of streptavidin can be achieved in a known matter by chemical treatment. Polymerized avidin or streptavidin and particularly preferably polymerized streptavidin is preferably used in a coating method according to the invention. Polymerized antibodies are also particularly suitable.

The above passage therefore provides support for polymerized streptavidin (and possibly also avidin) that has been polymerized by chemical treatment. There is no generic teaching in the specification of polymerization of *proteins in general* by chemical treatment. Although the specification refers to "polymerized proteins" at [0026], there is no mention of chemical treatment of "polymerized proteins" in the specification. Therefore, the recitation in claim 2 of "protein" that has been polymerized by chemical treatment represents the introduction of a subgenus of "proteins polymerized by chemical treatment" that is not supported by the disclosure of "streptavidin polymerized by chemical treatment".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the combination" in part (b). There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. (Vaynberg, K.A., Wagner, N.J., and Sharma, R. (2000) "Polyampholyte Gelatin Adsorption to Colloidal Latex: pH and Electrolyte Effects on Acrylic and Polystyrene Latices," *Biomacromolecules* **1**, 466-472) in light of Bocquier et al. (Bocquier AA, Potts JR, Pickford AR, Campbell ID (1999) "Solution Structure of a Pair of Modules from the Gelatin-Binding Domain of Fibronectin," *Structure* 7:1451-1460) and Bohidar ("Hydrodynamic properties of gelatin in dilute solutions" (1998) *International Journal of Biological Macromolecules* **23**:1-6).

Vaynberg et al. teach a method for producing protein-coated polystyrene microparticles that includes the steps of combining a suspension (colloid) of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair (gelatin), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation) (see p. 467, column 2, lines 30-32 and the section "Materials," lines 9-16; p. 468, column 1, lines 1-4, 15-31, and Table 1; p. 469, column 1, lines 1-7, and column 2, lines 25-29; and p. 470, Figure 8).

Vaynberg et al. do not specifically recite a reaction pH of pH 10.5 to 12.5. Rather, Vaynberg et al. teach adsorption of gelatin onto the polystyrene particles at various pH values up to pH 10 (Figures 1-7). However, MPEP 2144.05 notes that:

> ...a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)
>
> and further that:
>
> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)

In the instant case, it would have been obvious to one of ordinary skill in the art to employ slightly higher pH values (for example, pH 10.5) through routine optimization/ experimentation of the conditions of Vaynberg et al. with a reasonable expectation of success, because of the normal desire of scientists or artisans to improve upon what is already generally

known. In addition, one would be motivated to employ higher pH values because Vaynberg teaches that because hydrophobic effects dominate in adsorption of gelatin, increasing pH enables a denser layer of gelatin to form on the polystyrene (p. 471, left column, first full paragraph).

One would have reasonable expectation of success in employing higher pH values in the method of Vaynberg et al. because Vaynberg et al. repeatedly teach that pH differences were not critical and produced *little variation in the adsorption efficiency* of gelatin onto the polystyrene (p. 469, right column, line 25 to p. 470, left column and Figures 2-3). In particular, Vaynberg et al. teach that "pH hardly affects the adsorption of gelatin to [polystyrene]" (p. 470, left column, lines 12-13) and further note "the ability of gelatin to adsorb to [polystyrene] even at high electrolyte and high pH conditions" (p. 471, right column, second paragraph).

Vaynberg et al. also fail to teach adjusting the pH to the desired value after the microparticles are combined with the protein, as now recited in step (b) of claim 1. Rather, Vaynberg et al. teach adjusting the pH of the polystyrene microparticles and the gelatin prior to combining these two reagents (p. 468, left column, the first full paragraph). However, one skilled in the art would recognize that in order to carry out the coating reaction at the desired pH, the pH could be adjusted either before or just after mixing of the reaction components, so long as the mixture of reagents is at the desired pH while the coating reaction takes place. As such, it would have been obvious to one of ordinary skill in the art to manipulate the reaction pH either before or after mixing the components *in order to achieve the same purpose*, namely to maintain the reaction at the desired pH during the coating reaction. No criticality has been disclosed in the instant specification that would lead one skilled in the art to conclude that the pH must be

adjusted to the desired level *after* combining the microparticles with the protein vs. adjusting the pH prior to combination as in Vaynberg et al.

The Bocquier et al. and Bohidar et al. references are relied upon as evidentiary references teaching that the protein of Vaynberg et al., fulfills the limitations of being a partner of a bioaffinity binding pair and having a size from 10 nm to 300 nm as recited in claim 1. The protein gelatin is a partner of a bioaffinity binding pair as it binds fibronectin (see Bocquier et al., p. 1451, column 2, lines 1-10). Gelatin has a size within the recited range of 10 nm to 300 nm as evidenced by Bohidar, in particular at p. 4, Table 2. Bohidar evidences that gelatin has a size within the recited parameters since the radius values reported therein are in the recited range. In particular, the hydrodynamic radius $R_{e,D}$ is 190-280 Å, which is equivalent to 19.0-28.0 nm (Table 2).

9. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar as applied to claim 1 above, and in view of Tischer et al. (US Patent No. 5,061,640).

Vaynberg et al. is as discussed above, which fails to teach a protein that has been polymerized by chemical treatment.

Tischer et al. teach a process for the preparation of a protein for adsorption to an insoluble carrier material such as polystyrene (see column 2, lines 25-34 and column 4, lines 19-38). In particular, Tischer et al. teach polymerizing of proteins to be adsorbed using a cross-linking compound (column 3, lines 32-39 and 63-68; column 4, lines 1-7; column 8, Example 2, lines 38-42; and column 9, part (d), lines 9-10). Tischer et al. further teach that this polymerizing

of proteins has the effect of increasing their molecular weights (column 3, lines 32-43), which results in improved adsorption of the proteins to the insoluble carrier material (see column 2, lines 35-37).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the step of polymerizing gelatin by treatment with a cross-linking compound, as taught by Tischer et al., in the method for producing protein-coated microparticles of Vaynberg et al. in order to increase the molecular weight of gelatin and thereby improve the adsorption of gelatin to polystyrene. One would have reasonable expectation of success because Tischer et al. teach the step of increasing the molecular weight in preparation for coating proteins onto polystyrene by adsorption, which is the object of the method of Vaynberg et al.

10. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar as applied to claim 1 above, and in view of Desai et al. (US 6,638,728 B1).

Vaynberg et al. fail to teach a method where the protein coated is streptavidin that has been polymerized by chemical treatment.

Desai et al. (US 6,638,728 B1) teach methods for producing surfaces such as polystyrene spheres that are coated with streptavidin that has been polymerized by treatment with a chemical cross-linking reagent, (see in particular column 1, lines 25-30 and 60-67; column 2, lines 17-34; column 2, line 65 to column 3, line 24). Desai et al. teach that such surfaces are useful in capturing target molecules in assays (column 1, lines 53-59).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the method for producing protein-coated polystyrene microparticles of Vaynberg et al. to coat streptavidin that has been polymerized by chemical treatment, as taught by Desai et al. in order to produce microparticles that have a high capacity for capturing target molecules for use in assays. One would have reasonable expectation of success in employing the method of Vaynberg et al. with the polymerized streptavidin taught by Desai et al. because Desai et al. teach that polystyrene, which is the material taught in Vaynberg et al., is an appropriate solid phase for immobilization of polymerized streptavidin (see Desai at column 3, lines 42-44). In addition, while Vaynberg et al. only specifically teach the protein gelatin, Vaynberg et al. teach the adsorption of polyampholytes such as proteins in general (see p. 466, left column, first two paragraphs; and p. 471-472, "Conclusions").

11. Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable Lou et al. (US 4,329,151) in light of Rossjohn et al. ("Structure of a Cholesterol-Binding, Thiol-Activated Cytolysin and a Model of Its Membrane Form" *Cell* **89**:685-692 (1997) and Weis et al. ("Streptolysin O: the C-terminal, tryptophan-rich domain carries functional sites for both membrane binding and self-interaction but not for stable oligomerization" Biochimica et Biophysica Acta 1510 (2001) 292-299).

Lou et al. teach a method for producing protein-coated polystyrene latex microparticles, comprising combining a suspension of polystyrene latex particles with a protein (streptolysin-O) (see the abstract; column 2, lines 55-57; column 3, lines 40-62; column 6, lines 9-15 and 29-46). Lou et al. further teach incubating the combination of microparticles and protein in a buffer solution with a pH range of from about 8.5 to about 11.9 for a period of time whereby the protein

is coated onto the microparticles by adsorption (column 4, lines 34-43 and 49-63). Lou et al. further teach separating the non-adsorbed protein from the protein-coated microparticles by a wash step followed by centrifugation of the particles (column 5, lines 48-60). Streptolysin-O is a partner of a bioaffinity binding pair in that it is capable of binding to antibodies (column 1, lines 24-29).

Lou et al. teach that the coating reaction is maintained at the desired pH by diluting the protein into a buffered solution of the desired pH (column 4, lines 49-53; column 6, lines 29-31 and 40-42) before it is mixed with the microparticles. Therefore, Lou et al. fail to specifically teach that the step of adjusting the pH of the microparticle-protein combination.

However, as discussed above in regard to Vaynberg et al., it would have been obvious to one of ordinary skill in the art that maintaining the pH of the microparticle-protein combination during the coating reaction could be performed in several ways in order to achieve this same desired result. One skilled in the art would immediately envisage that the pH could be adjusted either before (as in Lou et al.) or just after mixing of the reaction components, so long as the mixture of reagents is at the desired pH while the coating reaction takes place. As such, it would have been obvious to one of ordinary skill in the art to manipulate the reaction pH either before or after mixing the components *in order to achieve the same purpose*, namely to maintain the reaction at the desired pH during the coating reaction. No criticality has been disclosed in the instant specification that would lead one skilled in the art to conclude that the pH must be adjusted to the desired level *after* combining the microparticles with the protein vs. adjusting the pH prior to combination as in Lou et al.

Lou et al. also fail to specifically state that the streptolysin-O has a size from 10 nm to 300 nm.

A search of the literature in order to determine the size of streptolysin-O protein found the Rossjohn et al. and Weis et al. references, which are relied upon to support the Examiner's position that the streptolysin-O protein used by Lou et al. does in fact have a size from 10 nm to 300 nm. Weis et al. teach that streptolysin-O belongs to a class of structurally related thiol-activated toxins (the abstract). While it appears that the exact size of streptolysin-O has not been determined by X-ray crystallography, Weis et al. teach that the X-ray structure another member of this class, perfringolysin-O, has been determined (Weis et al., p. 292; p. 295, Figure 1A and accompanying legend). In particular, Weis et al. teach that the structure of the streptolysin-O monomer has been modeled based on the crystal structure of the homologous perfringolysin-O. Thus, Weis et al. teach that the structure of streptolysin-O may be approximated based on the structure of perfringolysin-O since these proteins are highly homologous.

Rossjohn et al. is the publication referred to by Weis et al. as describing the structure of perfringolysin-O (Weis et al., p. 292). Rossjohn et al. also teach that perfringolysin-O is a member of a class of toxins (including streptolysin-O) that are highly homologous, "suggesting they will all have very similar 3D structures" (p. 685, "Introduction"). Rossjohn et al. teach that perfringolysin-O is an unusually elongated rod-shaped molecule with dimensions of 115 x 30 x 55 Angstroms (p. 685, right column, "Overall Structural Features"). Since 1 Angstrom = 0.1 nm, perfringolysin-O has dimensions of 11.5 x 3 x 5.5 nm, which are within the claimed size range of 10 nm to 300 nm. In light of the teaching in Weis et al. that the structure of streptolysin-O may be inferred by reference to the structure of perfringolysin-O, and also the teaching in Rossjohn et

al. that the toxin family members are expected to have very similar 3D structures, one skilled in the art would reasonably conclude that streptolysin-O has very similar dimensions to that of perfringolysin-O and therefore meets the claimed size range.

With regard to claim 2, the streptolysin-O protein of Lou et al. is polymerized (cross-linked) by addition of a carbodiimide chemical compound (column 3, lines 48-62; column 5, lines 48-54).

12. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vaynberg et al. in light of Bocquier et al. and Bohidar, or, alternatively, over Lou et al. in light of Weis et al. and Rossjohn et al., and further in view of Bangs ("New developments in particle-based immunoassays: introduction" (1996) *Pure & Appl. Chem.* **10**:1873-1879). Vaynberg et al. and Lou et al. are as discussed above, which fails to teach microparticles that have a magnetizable core.

However, Bangs teaches microparticles that have a magnetizable core (superparamagnetic particles and magnetic microspheres; see p. 1873, "Introduction," lines 1-4 and p. 1876, "Superparamagnetic Particle Based Assays") and their utility in fast and easy separation of solid and liquid phases, since they can be used to pull things out of solution quickly. The magnetic microparticles can be used in a variety of solid phase assays including ELISA and RIA.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the microparticles having a magnetizable core as taught by Bangs in the method for producing protein-coated polystyrene microparticles of Vaynberg et al. or,

alternatively, Lou et al. because Bangs teaches the convenience of such microparticles in the fast and easy separation of solid and liquid phases. One would have a reasonable expectation of success because Bangs et al. teach that magnetic microparticles can be used in various types of solid phase assays.

Response to Arguments

Applicant's amendments and arguments in the amendment filed 2/21/06 have been fully considered.

With regard to the rejection of claim 1 under 35 USC 103(a) above, Applicant's arguments (p. 6-8) have been fully considered but they are not persuasive. Applicant argues that Vaynberg does not motivate the skilled artisan to assess coatings at pH values higher than 10, e.g., at pH 10.5. In particular, Applicant first argues that because Vaynberg explicitly teaches that the maximum adsorption is around pH 6.2 for coating of polystyrene particles, there is clearly no motivation for the skilled artisan to test the pH range beyond pH 10 (Applicant's response, p. 6, the last paragraph). While the Examiner agrees that Vaynberg et al. report a maximum pH of adsorption to polystyrene, this teaching must be read in the context of the reference as a whole, which establishes that although a "maximum" adsorption was achieved at this pH, the levels of adsorption achieved at other pH values was very close to this maximum, and that there was in fact little variation at widely varying pH values.

This is apparent when the statement in which the maximum pH of 6.2 is reported is read in context. Vaynberg et al. state that:

> In contrast, *the effect of pH on gelatin adsorption to [polystyrene] is noticeably weaker*, with a maximum around pH = 6.2. Note that the pH effects are solely attributed to the changes occurring within the gelatin, *as the surface charge of the colloids does not change in the pH interval studied...*" (p. 469, left column; emphasis added)

The Examiner has considered the reference as a whole, balancing the above teaching of a "maximum pH" with its interpretation by Vaynberg et al. at several points throughout the reference. For example, the data that produced the maximum pH cited by Applicant (and shown in Figure 2 of Vaynberg et al.) are discussed further by the authors in the paragraph that bridges p. 469-470:

Returning to our data for the pH variation of the adsorption of gelatin on PS, **we observe little variation of the adsorption equilibrium constant with pH**. This confirms earlier conclusions that gelatin adsorption on [polystyrene] is dominated by the hydrophobic interactions, such that direct electrostatic effects are secondary. (emphasis added)

Further, at p. 470, left column, "Adsorption Isotherms", Vaynberg et al. teach that:

We observe that the saturation coverage on acrylic latex decreases with the pH...In contrast, **pH hardly affects the adsorption of gelatin to [polystyrene]...pH variations do not affect gelatin adsorption to strongly hydrophobic substrates**.

At p. 471, right column, the second paragraph, Vaynberg et al. again refer to "the ability of gelatin to adsorb to [polystyrene] even at high electrolyte and high pH conditions".

Thus, although Vaynberg et al. have reported a maximum adsorption is around pH 6.2, the authors repeatedly emphasize that there was, in fact, "little variation" in adsorption among the different pH values studied, and that "pH hardly affects the adsorption". There is no teaching that adsorption is significantly affected at other pH values other than pH 6.2, and there is similarly no teaching that pH 6.2 represented a dramatic improvement over the other pH values tested, for example. Therefore, Vaynberg et al. provide the skilled artisan with a reasonable expectation of success in using the method over a wide range of pH values. While Vaynberg et al. do not specifically direct one to perform the method at pH values greater than 10, it would have been obvious to one of ordinary skill in the art to employ a slightly higher pH of 10.5 out of

the normal desire of scientists or artisans to improve upon what is already generally known, and especially in light of the teaching by Vaynberg et al. that increasing pH enables a denser layer of gelatin to form on polystyrene, as noted above.

With regard to Applicant's arguments that the teachings should not be extrapolated beyond the pH values actually tested and reported by Vaynberg et al. (p. 7-8), this argument is not found persuasive in light of the broad range of pH values tested in Vaynberg et al., none of which uncovered evidence that altering pH would significantly impact adsorption levels. Extrapolating from data collected in order to interpret and draw conclusions from the data is a familiar practice to one skilled in the art, and this is in fact done by Vaynberg et al., who extrapolate from the data collected in order to discuss trends observed in terms of *increasing and decreasing pH* and not in terms of the specific pH data points collected (see for example at p. 471, left column, the first full paragraph).

With regard to Applicant's argument that an increase in pH from 10 (as in Vaynberg et al.) to 10.5 (as in the claimed invention) is not a "slightly higher" pH, the Examiner acquiesces with Applicant regarding the logarithmic nature of the pH scale. However, the Examiner disagrees that the skilled artisan would not be motivated to perform such an increase, particularly when the broad range of pH values evaluated by Vaynberg et al. is taken into account. For example, in Figure 8 of Vaynberg et al., a scale from pH 4 to pH 12 is depicted. Although it appears that only data up to pH 10 were actually collected, when this broad range of pH values is considered, an increase of 0.5 pH units would not be beyond the scope of the skilled artisan.

With regard to the rejections of claims 2, 3, and 5, Applicant's response did not include any specific arguments regarding the rejections of record (see p. 8).

Conclusion

13. No claims are allowed.

The following references not relied upon above are also cited by the examiner as prior art of relevance:

Spaeth et al. ("Studies on the Biotin-Avidin Multilayer Adsorption by Spectroscopic Ellipsometry" *Journal of Colloid and Interface Science* **196**, 128-135 (1997)) is cited for its teaching, like Desai et al. above, of streptavidin polymerized by chemical treatment and the use of such a reagent in preparing affinity surfaces used in clinical immunoassays (p. 129, right column, "Materials and Methods").

Morgan et al. ("Modeling the Bacterial Protein Toxin, Pneumolysin, in Its Monomeric and Oligomeric Form" *Journal of Biological Chemistry* **269** 25315-25320 (1994)) is cited for its teaching of pneumolysin, which is a member of the family of related bacterial thiol-activated toxins that include streptolysin-O taught by Lou et al. above. Morgan et al. teach in particular that pneumolysin has an overall projected length of 12.56 nm (p. 23517, left column, "Molecular Shape of Pneumolysin").

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

cfoster

Christine Foster, Ph.D.
Patent Examiner
Art Unit 1641

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
03/30/06